PATENT

Attorney Docket No. 11823-002630

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: J. Reeves
CARY L. QUEEN ET AL.	Art Unit: 1642
Application No.: 08/484,537	
Filed: June 7, 1995	DECLARATION UNDER 37 C.F.R. 1.132
For: IMPROVED HUMANIZED IMMUNOGLOBULINS	

#38

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DECLARATION OF CARY L. QUEEN

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Cary L. Queen, declare and state as follows:

1. I have described my background and qualifications in my previous declaration, and provided a copy of my curriculum vitae. I am a named inventor of the subject patent application. I have read the Office Action dated Nov. 4, 1999 and previous office actions in the subject case.

2. In my previous declaration I explained that immunoglobulin variable region framework sequences (Ig sequences) can be aligned unambiguously, generally without gaps, according to the numbering system of Kabat. Moreover, one of skill in the art would naturally align any two variable region framework sequences by Kabat numbering.

3. I submitted as Exhibit 2 with my previous declaration a listing from Kabat et al. of Ig sequences, which shows how they can be aligned unambiguously by Kabat numbering. However, as Exhibit 2 only shows *human* Ig sequences, the Examiner questions whether

rodent sequences can be aligned in this manner with human sequences, as required to practice the claimed method.

4. In fact, the same Kabat numbering system is applicable to Ig sequences from both human *and* rodent species (e.g., mouse, rat, rabbit) as well as the other species listed in the Kabat et al. compendium. To make this point clear, I have prepared a composite listing which contains both representative **human** Ig sequences (from subgroup I) and representative **mouse** sequences (from subgroup IIA), which is attached here as Exhibit A. I prepared this exhibit by copying the two relevant pages from Kabat et al., with one overlapping the other.

5. As can be readily seen from Exhibit A, Kabat uses exactly the same numbering system for mouse as for human Ig sequences. For example, for both human and mouse sequences, the four heavy chain framework segments constitute the following amino acid numbers: FR1, 1 - 30; FR2, 36 - 49; FR3, 66 - 94; FR4, 103 - 113. The intervening CDRs also have the same numbering for human and mouse sequences. Hence, the Kabat numbering system provides a unique method of aligning a human Ig framework sequence *with* a mouse Ig framework sequence.

6. Moreover, as can also be seen from Exhibit A, not only are there no gaps in the frameworks of the human and mouse sequences when compared within species, there are also no gaps when the human framework sequences are aligned with the mouse framework sequences -- every position contains an amino acid. (Of course, there are gaps within the CDRs). Indeed, Exhibit A illustrates how the Kabat numbering system provides a unique way of aligning human and mouse framework sequences without gaps. Thus, as explained in my previous declaration, the issue of gap weights, etc. does not arise for Ig framework sequences.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dated: Cary Owen 12/21/99

PATENT

Attorney Docket No. 11823-006800

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
John Robert Adair et al.	Examiner: L. Feisee
Serial No.: Unknown	Art Unit: 1806
Filed: Unknown	DECLARATION UNDER 37 CFR §1.132 SUBMITTED WITH PROTEST UNDER 37 CFR §1.291
For: HUMANISED IMMUNOGLOBULINS	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Cary L. Queen, declare and state as follows:

1. I received my Ph.D. in 1975 from the University of California, Berkeley. I am an author of over 40 publications, many of which report on research in molecular immunology. A copy of my curriculum vitae is attached as Exhibit 1.

2. I am Vice President, Research at Protein Design Labs, Inc. (PDL), Mountain View, California. In this capacity, one of my primary responsibilities is directing PDL's immunoglobulin humanization program. I am also a co-inventor of U.S. Patent Nos. 5,530,101 and 5,585,089 (the '089 patent).

3. I have reviewed WO91/09967 (the Adair application) and determined which framework substitutions from the OKT3 mouse antibody were made in the preferred humanized OKT3 antibody. Specifically, the preferred humanized OKT3 variant has four light chain substitutions at positions 1, 3, 46 and 47, and eleven heavy chain substitutions at positions 6, 23, 24, 48, 49, 71, 73, 76, 78, 88 and 91, outside the Kabat and Chothia CDRs (please refer to light chain 221A and heavy chain 341A in Table 1 on p. 41 of the Adair application). In my opinion, each substitution is deducible from the criteria set forth in, e.g., the '089 patent, except for the heavy chain position 6 change.

4. To confirm this, under my supervision PDL scientists modeled the OKT3 antibody variable domain using the procedures described in the '089 patent (column 15, lines 48-53). With this model and using computer graphics software described in the '089 patent (column 15, lines 58-62), we determined those OKT3 framework amino acids which were capable of interacting with amino acids in the Kabat and Chothia CDRs. By inspection of the sequence, we also determined these amino acids adjacent to the CDRs. We further analyzed typical and rare amino acids by reference to a sequence data bank. We then prepared the appended Table, which demonstrates that all 4 substituted positions in the humanized OKT3 light chain and 10 of the 11 such positions in the OKT3 heavy chain meet at least one criterion specified in the '089 patent.

5. We also prepared color photographs of a computer- generated model of the OKT3 antibody variable domain to illustrate the relationships. Appended Figure 1A is a front view of the model in wireframe form, in which the light chain is on the left and the heavy chain is on the right. Appended Figure 1B is the same model in rear view, so the light chain is now on the right. Appended Figure 2A is a front view of the model in space-filling form. Similarly, appended Figure 2B is a rear view of the same model in space-filling form. We have colored red the Kabat and Chothia CDRs. Moreover, we identified and colored blue any amino acids that were substituted in the Adair application and which we believe are capable of interacting with the CDRs. These are labeled using a standard labeling scheme, for example, CB (73H Lys) means the amino acid lysine at heavy chain position 73. We also colored yellow amino acids 88H and 91H, where a rare amino acid is substituted by a common one.

6. The appended photographs demonstrate that the blue amino acids (i.e., those we identified as capable of interacting with the CDRs) are in fact close to the CDRs, with our computer-aided measurements indicating such amino acids to have an atom within 6 Å of the CDRs.

7. In my opinion, the amino acid substitution at heavy chain position 6 (colored magenta in the photos) is not significant. This substitution's contribution to the affinity of humanized OKT3 is unknown, as the Adair application only shows that the group of substitutions at 6, 23 and 24 contribute. And, I believe that amino acids 23 and 24 (which are capable of interacting with the CDRs) are more likely to contribute to binding

(instead of the distant amino acid 6). Moreover, the Adair application never shows that a position 6 substitution contributes to the affinity of other humanized antibodies. Hence, in my opinion, such a substitution is probably only a design choice.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

Dated: 3/19/97

Cary Queen
Dr. Cary Queen

#35 Attach

Attorney Docket No.: 11823-002630US

12/23/99

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **IMPROVED HUMANIZED IMMUNOGLOBULINS** the specification of which ____ is attached hereto or _X_ was filed on **June 7, 1995** as Application No. **08/484.537** and was amended on January 3, 1997, July 21, 1997, May 14, 1998, August 11, 1998, and August 9, 1999.

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56. I claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Country	Application No.	Date of Filing	Priority Claimed Under 35 USC 119

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date

I claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application No.	Date of Filing	Status
07/290,975	December 28, 1988	Abandoned
07/310,252	February 13, 1989	Abandoned
07/590,274	September 28, 1990	Abandoned
07/634,278	December 19, 1990	Issued as U.S. Patent 5,530,101 on June 25, 1996

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1	Signature of Inventor 2
CARY L. QUEEN	X  **HAROLD E. SELICK**
Date	Date X 12/16/99

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